REMARKS

In the outstanding Office action, claims 1-7 and 9-30 were presented for examination. Claims 1-7 and 9-23 were rejected. Claims 24-30 were not mentioned in the Office action.

In this amendment, applicant has amended claims 1 and 9. Accordingly, claims 1-8 and 9-30 are now pending for examination and, as will be discussed in detail below, it is believed that the application is in condition for allowance. Applicant notes that the supplemental amendment filed November 19, 2007, in which new claims 24-30 were presented, was not considered in the outstanding Office action. Favorable consideration, or reconsideration of all claims now pending is respectfully requested.

The Examiner's courtesies during the telephone interview on March 6, 2008, and in mailing a corrected Office action, are appreciated by applicant. The withdrawal of objections and rejections not reiterated and the acknowledgment of applicant's priority date are also appreciated by applicant.

Specification

The specification has been amended, on page 6, to explain the terms used in equations (8) and (9) appearing on page 6. The explanations now set forth are believed to be implicit in applicant's specification as filed as the specification would have been understood by a person of ordinary skill in the art in light of their knowledge of the art, including Y. Matveev et. al. in Food Hydrocolloids Vol. 11 no. 2 pp. 125-133, 1997 ("Matveev et al."), cited on page 6 of the specification. The Office's attention is respectfully drawn to the first sentence on page 125 and to the lefthand column of page 127 of the Matveev et al. document.

Claim Amendments

Claim 1 has been amended, without narrowing, to more explicitly set forth the method according to Matveev et al. of calculating the glass transition temperature of the polypeptide recited in claim 1, which method was referenced in claim 1 as it appeared before this amendment. Support for this amendment can be found at page 6, line 6 to the end of the table appearing on page 7 of applicant's specification.

Claim 9 has been amended in a similar manner to claim 1 and the amendment made is similarly supported. In addition, claim 9 has been amended to more explicitly recite the lyophilizing process claimed.

Claim Rejections - 35 U.S.C. § 112 First Paragraph

Claims 1 and 9 were rejected under 35 U.S.C. § 112 first paragraph for allegedly failing to comply with the written description requirement owing to the inclusion in claims 1 and 9 of reference to a method of calculation set forth in a publication identified in the claim, which reference was deemed improper.

Without acquiescing to the rejection, and to expedite prosecution, claims 1 and 9 have been amended to recite the relevant specific equations (formulae) disclosed in the Matveev et al. reference to calculate the glass transition temperature of a polypeptide. As explained above, amended claims 1 and 9 are supported by the description on page 6 of applicant's specification. To make the calculation, a skilled person can determine the amino acid content of a polypeptide. With this knowledge, the skilled person will know the number of amino acid residues of the *i*th type in the polypeptide and can determine the corresponding $T_{g,i}$ and ΔV_i from values given in the table in the application, can accumulate the partial values and can use these partial values in Equations (8) and (9) to calculate a glass transition temperature for the polypeptide.

Accordingly, applicant believes new claims 1 and 9 as well as claims 2-7, which depend from claim 1, and claims 10-23 which depend from claim 9, are compliant with the written description requirement. Favorable reconsideration is respectfully requested.

Claim Rejections - 35 U.S.C. § 103 Alleged Unpatentability

In the outstanding Office action, claims 1-7, 9-23 were rejected under 35 U.S.C. § 103 as allegedly being unpatentable over International Publication No. WO 01/34801, referenced as "Chang et al." in view of Matveev et al. (*supra*).

In reply, applicant respectfully submits that claims 1 and 9, along with claims 2-7 and claims 10-30 which depend from claims 1 and 9, respectively, are patentably distinguished from any combination of Chang et al. and Matveev et al., and are therefore allowable, for reasons which will now be explained.

As a prefatory matter, applicant notes that on pages 5 and 6 of the Office action there are several references to a Tg of 200° C, indicating in at least one instance that applicant's claims recite a polypeptide having a Tg of 200° C. In fact, applicant's independent claims 1 and 9 recite a calculated glass transition temperature of higher than 180 degrees Celsius, while claims 21-23 recite that the calculated glass transition temperature is higher than 200 degrees Celsius. Unless the context indicates otherwise, the following remarks are believed applicable to applicant's amended claims 1 and 9 which recite a calculated glass transition temperature of higher than 180 degrees Celsius.

As for the outstanding rejection, at page 65, lines 21–25, Chang et al. mentions that recombinant gelatins for vaccine formulations have characteristics similar to those of hydrolyzed animal-source gelatin, for example, "similar molecular weights, melting temperatures etc."

As applicant understands the Office action, it is the Office's position in support of the rejection that a person of ordinary skill in the art would combine the above disclosure in Chang et al. with the mention in Matveev et al. that gelatin can have a glass transition temperature of 200 °C, and conclude that recombinant gelatin can be derived from animal sources and can have characteristics similar to those of animal-source gelatin including a glass transition temperature of 200 °C as is disclosed in Matveev et al.

In response, applicant respectfully submits that the invention claimed in amended independent claims 1 and 9 provides the benefit of an improved stability of the claimed composition or of the composition produced by the claimed process. This result is not predictable from either Chang et al. or Matveev et al. neither of which document indicates that the stability of a lyophilized composition comprising a physiologically active agent can be improved by employing a recombinant or synthetic polypeptide in the composition. Accordingly, claims 1 and

9 are believed to be unobvious and therefore patentable for this reason alone. Knowledge of the relationship between the glass transition temperature and the improved stability is an element missing from the combination of Chang et al. with Matveev et al.

Also, applicant believes that a person of ordinary skill in the art, following Chang et al.'s suggestion to employ a recombinant gelatin having similar properties to gelatin isolated from animals and looking at the glass transition temperatures mentioned in Matveev et al. would not be able to provide the claimed composition and method because Chang et al. does not appear to disclose a method of preparing a recombinant or synthetic gelatin-like polypeptide meeting the requirements of applicant's claims 1 and 9 with regard to a calculated glass transition temperature of higher than 180 degrees Celsius. Accordingly, amended claims 1 and 9 are believed further patentable for this additional reason.

As disclosed in applicant's specification, at page 5, lines 7-26 and at page 8, line 13 to page 9, line 6, applicant has determined that a new recombinant or synthetic gelatin with an increased calculated glass transition temperature can comprise a sequence identical to, or highly homologous to, a native polypeptide sequence, for example, a human collagen sequence. The location of the native polypeptide sequence in the native molecule can be identified by using moving averages of calculated glass transition temperatures, as described in the specification. A sequence can be selected which has, for example, a calculated average glass transition temperature of about 10 degrees Celsius, or more, higher than the calculated average collagen glass transition temperature of the complete native starting sequence.

Neither Chang et al. nor Matveev et al. appears to disclose or suggest that a native polypeptide sequence can include a region that has a calculated glass transition temperature which is higher than that of the complete sequence of the native polypeptide, and that this region can be identified and utilized to improve the stability of vaccines and other physiologically active products.

In further support of the rejection, the Office action states, on page 5, that disclosed examples and preferred embodiments in Chang et al. do not constitute a teaching away from a broader disclosure of non-preferred embodiments, citing *In re Susi*.

Applicant does not disagree, but believes that the disclosure of Chang et al. considered as a whole teaches a skilled person that essentially any recombinantly produced collagen or gelatin can be employed in vaccine compositions. Thus, while Chang et al. may disclose that polypeptides having various molecular weights, degrees of hydroxylation and/or cross-linking can be employed in vaccine compositions, Chang et al. does not appear to disclose that a higher polypeptide glass transition temperature can improve vaccine stability. Nor does Chang et al. appear to provide a method of producing a recombinant gelatin-like polypeptide as defined in applicant's amended claims 1 and 9 which recite a calculated glass transition temperature higher than 180 degrees Celsius.

To better understand Chang et al.'s teaching regarding the role of the gelatin glass transition temperature or melting point, below applicant discusses passages which applicant has identified in Chang et al. that mention an increase or decrease in melting point of the described gelatins or an effect resulting from an increase or decrease in melting point.

At page 35, line 37 to page 36, line 6, Chang et al. describe that the melting point and/or gel strength of a recombinant gelatin can be manipulated in a variety of ways, and that the temperature stability and/or gel strength of recombinant gelatin can be measured by a variety of techniques well known in the art.

At page 36, lines 8-17, Chang et al. teaches that the methods of the Chang et al. invention can produce high molecular weight gelatins that have a lower melting point than animal-source gelatins.

At page 37, lines 22–23, Chang et al. mentions that a higher degree of cross-linking results in gelatins with higher melting temperatures and greater gel strength. However, Chang et al. is silent as to the stability of such cross-linked gelatins.

According to Chang et al., at page 59, line 30 et seq., stability is a critical issue in vaccine development. To provide vaccine stability, Chang et al. suggests, at page 62, lines 21 and 29, and page 64, line 22, using recombinant human gelatin. The melting point of the recombinant human gelatin to be used does not appear to be mentioned by Chang et al. as a factor relevant to vaccine stabilization.

The melting point of the recombinant gelatin described in Chang et al. is referenced in a general manner at page 65, lines 22-24, where it is stated that recombinant gelatin can have characteristics similar to those of hydrolyzed animal-source gelatin, e.g. similar molecular weights, melting temperatures etc. Again, there appears to be no mention here, or elsewhere in Chang et al., of any effect of melting point on vaccine stability, either pro or con.

As explained above, applicant has been unable to find any disclosure in Chang et al. that would teach a skilled person that the stability of a vaccine or other lyophilized compositions comprising a physiologically active substance could be improved by increasing the melting point or glass transition temperature of a recombinant gelatin-like polypeptide employed in the composition.

Moreover, applicant does not believe that the use of a gelatin-like polypeptide meeting the requirements of amended claims 1 and 9 is an obvious alternative to a use of animal-derived gelatin suggested by Chang et al., as appears to be suggested on page 6 of the Office action. The reason for this belief is that Chang et al. itself teaches, at page 62 lines 8–25, the desirability of avoiding animal-derived gelatin. Again, at page 63, lines 5-7, Chang et al. describes its invention as "providing a gelatin material without . . . . the risks associated with animal-derived materials, . . ." Accordingly, applicant believes that a skilled person following the teachings of Chang et al. would not employ animal-derived gelatin, notwithstanding the teachings of Matveev et al. Also, as is further explained below, in the section entitled "End Note", applicant respectfully does not understand the suggestion that a recombinant gelatin can be "derived from animal sources". However, this point does not appear to be material to the patentability of applicant's claimed invention.

With regard to *In re Fulton*, which is relied upon in the Office action, applicant's claims are not reliant for patentability upon Chang et al.'s teaching away from the claimed invention. Rather, applicant believes that even when combined with Matveev et al., Chang et al. does not provide the claimed invention because Chang et al. does not disclose the desirability of a higher glass transition temperature for improving the stability of vaccines or other physiologically active agents. Furthermore, Chang et al. does not appear to describe the manufacture of a polypeptide having a calculated glass transition temperature in excess of 180 degrees Celsius, as recited in applicant's claims 1 and 9, and applicant doubts whether Chang et al.'s methods can provide such a polypeptide. Accordingly, it is doubtful whether Chang et al. enables the making of the polypeptide recited in applicant's claims 1 and 9.

As has been explained, even if a skilled person were to consult Matveev et al., in spite of the disadvantages associated with the animal source gelatins, combining Matveev et al. with Chang et al. still does not appear to point to the improved stability of a physiologically active agent such as a vaccine which can be obtained with an increased glass transition temperature, pursuant to applicant's claimed invention. Matveev et al. appears only to describe, at page 132, under the heading **"**Conclusions**"**, a connection between glass transition temperature increase and compatibility issues in terms which do not appear to be relevant to applicant's claimed invention.

In further support of applicant's conclusion that Chang et al. does not enable the preparation of a recombinant gelatin with a calculated glass transition temperature higher than 180 degrees Celsius, applicant asserts that all the examples of Chang et al. relate to recombinant gelatins having calculated glass transition temperatures lower than 180 ^{o}C. In a previous paper, applicant provided the calculated glass transition temperatures for sequences 15, 25, 30, 31 and 33 of Chang et al.. A new listing below provides the calculated glass transition temperature for the remaining sequences in Chang et al.'s examples, each of which exhibits a calculated glass transition temperature lower than 180 ^{o}C.

Chang et al. SEQ ID No.:	**Calculated Tg (deg C) according to the method of Matveev**

15	124.2
25	164.3
30	137.5
31	156.3
33	174.1
16	143.3
17	162.1
18	118.4
19	139.6
20	149.4
21	151.5
22	168.3
23	139.9
24	146.0
26	167.5
27	155.6
28	148.6
29	124.8

Accordingly, applicant does not believe that a person of ordinary skill in the art at the time of the invention who was seeking to improve the stability of a lyophilized composition comprising a physiologically active substance and a stabilizer, and who followed the teaching of Chang et al., as illuminated by Matveev et al., would expect to succeed by employing a recombinant polypeptide having a calculated glass transition temperature higher than 180 degrees Celsius, or would know how to make such a recombinant polypeptide. For these reasons and for the reasons set forth above, applicant respectfully submits that amended claims 1 and 9 are unobvious, and therefore are patentable.

Dependent Claims

Claims 2-7 which depend from claim 1, and claims 10-30 which depend from claim 9, incorporate all the limitations of their parent claims and therefore are believed allowable for at least the same reasons that claims 1 and 9 are believed allowable. Dependent claims 2-7 also are believed clearly and patentably distinguished from the art of record, and therefore allowable, by the additional limitations they recite.

For example, claims 5 and 12-14 specifically recite that the polypeptide has a bimodal molecular weight distribution which does not appear to be disclosed or suggested by Chang et al., Matveev et al., or any of the other art of record in this application.

Also, claims 21-23 specifically recite that the (calculated) glass transition temperature of the recombinant or synthetic gelatin-like polypeptide recited in claim 1, 2 or 3, respectively, is higher than 200 degrees Celsius which applicant believes is neither disclosed nor suggested by Chang et al, Matveev et al. or any of the other art of record in this application. Matveev et al., in Tables 2 and 4, reports a food gelatin as having a calculated glass transition temperature of 200 ^{o}C, but does not appear to describe a gelatin having a higher glass transition temperature, regardless of the source of the gelatin. (As noted below under the heading "End Note", the glass transition temperature of 217 ^{o}C in Table 4 is an experimental figure, not a calculated figure).

Claim 26 recites that the recombinant or synthetic gelatin-like polypeptide has a calculated average glass transition temperature higher than the calculated average glass transition temperature of a similar native collagen by an amount of about 10 degrees Celsius or more, all as defined in claim 26 and its parent claims. Neither Chang et al. nor Matveev et al. appears to disclose this subject matter.

Further, claim 28 recites that the recombinant or synthetic gelatin-like polypeptide is similar to a native collagen amino acid sequence. The native collagen amino acid sequence has a calculated moving average glass transition temperature along the native collagen amino acid sequence with a value for the amino acid region of the native collagen of at least about 10 degrees Celsius higher than the calculated average collagen glass transition temperature of the complete native collagen. Neither Chang et al. nor Matveev et al. appears to disclose or suggest this subject matter.

End Note

For the record, applicant notes that page 4 of the Office action states that Matveev et al. teaches that the glass transition temperature of gelatin is 200-217^{o} C, citing pages 129 and 132. Applicant respectfully believes this characterization of Matveev et al. is inaccurate. At the foot of

each of the tables on pages 129 and 132 of Matveev et al., a calculated T_g of 200 °C is shown. However, no range of 200-217 °C appears to be shown. Table 4 on page 133 also shows an experimental T_g of 217 °C for a gelatin food protein, but this is not a calculated T_g, as is required by applicant's claims.

Page 4 of the Office action also references a "recombinant gelatin derived from an animal source" and states that "Chang et al. disclose vaccines can be formulated from recombinant gelatin derived from an acceptable mammalian source (claims 1-7, 9-23)". However, it is not clear to applicant how the recombinant gelatin is purportedly "derived" from animal sources. Recombinant polypeptides are not produced by extraction from an animal source. Rather they are usually produced in the laboratory, or in equivalent industrial processes, by expression from microorganisms or by in vitro biosynthesis. Thus, applicant respectfully does not understand in what sense Chang et al.'s recombinant gelatin is considered to be "derived" from an animal source.

Furthermore, for completeness, applicant notes that the reference on page 6 of the Office action to recombinant gelatin possibly being derived from animal sources is respectfully not understood. Neither applicant's claimed recombinant polypeptide, nor Chang et al.'s recombinant gelatin appears to be derived by isolation from animal (mammal) sources. Rather, the polypeptides such as are recited in applicant's claims can be prepared by expression of recombinant genes in microorganisms such as yeast, or can be prepared synthetically. Also the statement on page 6 of the Office action that it would be reasonable for one of ordinary skill to recognize that food grade gelatin is derived from an animal source, does not appear to be relevant to applicant's claimed invention. None of the foregoing points is believed material to the patentability of applicant's invention as it is now claimed. However, the Office is respectfully requested to provide clarification if any of these conclusions or assertions is to be relied upon in a future action.

Conclusion

In view of the above amendments and the discussion relating thereto, it is respectfully submitted that the instant application, as amended, is in condition for allowance. Favorable reconsideration and allowance are earnestly solicited. If for any reason the Examiner feels that

consultation with applicant's representative would be helpful in the advancement of the prosecution, the Examiner is invited to contact the undersigned practitioner.

Respectfully submitted,

By: /Roger Pitt/
Roger Pitt
Reg. No. 46,996 Ph: (212) 536-4867

(Customer Number 00545)
K&L GATES LLP
599 Lexington Avenue (33rd Floor)
New York, NY 10022-6030